

CASE REPORT

## Glioblastoma management: challenges in the elderly population

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Glioblastoma is a highly aggressive and generally lethal brain tumor despite aggressive treatment. Treatment to ensure prolonged survival while maintaining quality of life has always been challenging, as glioblastoma occurs mostly in elderly population who already have multiple comorbidities. We present the case of a 75-year-old male who was evaluated for complaints of recurrent falls due to gait abnormalities and weakness, and was found to have multifocal glioblastoma. Despite rapid initiation of chemo radiation, he did not respond to therapy and died within 4 months of diagnosis.

Keywords: *brain tumor; elderly; glioblastoma; MGMT; temozolomide*

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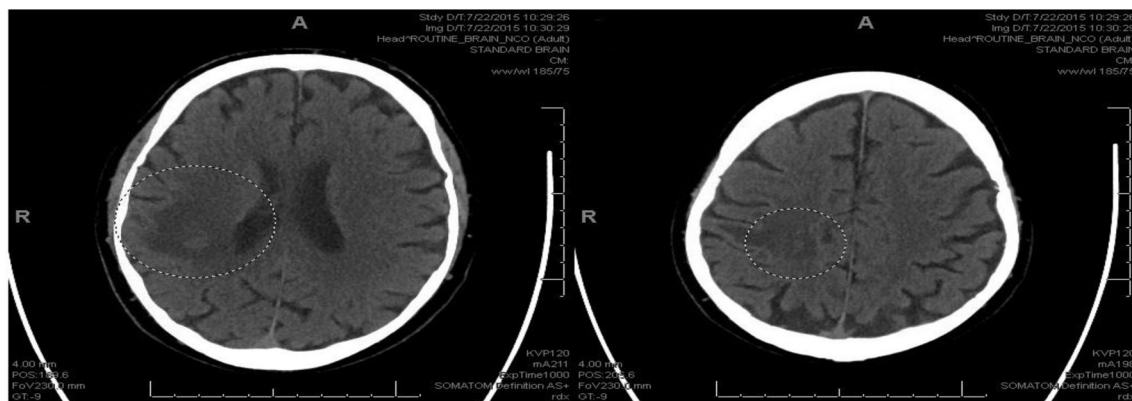
Glioblastoma, also commonly referred to as glioblastoma multiforme (GBM), is the most common and most aggressive primary malignant tumor of the central nervous system (1, 2). More than 10,000 new cases are diagnosed every year in the United States (US) (2). The incidence of glioblastoma increases with age and the median age at diagnosis is 64 years (1). Despite aggressive treatment with surgery, radiation, and chemotherapy, median survival is only about 15 months (1, 2). The fact that it occurs mostly in the elderly who already have many comorbidities makes the management even more challenging, and treatment should be tailored to balance survival and quality of life (1, 3).

### Case report

A 75-year-old male with a history of essential hypertension, hyperlipidemia, and newly diagnosed type 2 diabetes mellitus presented to the office with complaint of generalized fatigue and worsening neurological symptoms of 4 weeks' duration, which he attributed to the new start of metformin for his diabetes mellitus. He reported increasing muscle weakness along with poor coordination and recurrent falls to the left side. He had fallen not only while standing but also while getting on his bicycle. He had been experiencing difficulty turning his head either way sideways, along with difficulty turning the steering wheel of his recreational vehicle to the left side. Other symptoms included hoarse voice, dysphagia for solids and liquids,

difficulty writing on a straight line, and difficulty typing on his keyboard. In the 6 weeks since his last office visit, he had lost 17 pounds, but denied fever, chills, night sweats, tick bite, or head trauma. There was no personal or family history of malignancy. He was a recently retired ophthalmologist with no recent travel and was a lifelong non-smoker.

On examination, he was afebrile and hemodynamically stable. He was alert and oriented to time, place, and person. There was left facial drooping but no sensory or other cranial nerve deficits. A wide-based stumbling gait with left foot drop was evident. Motor strength was decreased on left side compared to right, Babinski was equivocal on left side and deep tendon reflexes were 1+ throughout. He had decreased fine motor control with rapid finger movements and illegible signature, but cerebellar signs were otherwise normal. Routine blood tests, including complete blood count, basic metabolic panel, electrolytes, C-reactive protein, and coagulation profile, were unremarkable. Lyme antibody by ELISA was negative. Computed tomography (CT) of head revealed two focal lesions in right frontoparietal region with surrounding edema as shown in Fig. 1. Magnetic resonance imaging (MRI) brain revealed a total of five enhancing lesions: two in right parietal region, one in each cerebral peduncle, and one in right basal ganglia with adjacent edema as shown in Fig. 2. Differential diagnoses included metastatic disease to brain, lymphoma, or abscesses. CT of chest, abdomen, and pelvis to look for



*Fig. 1.* Axial CT head showing focal lesion in right parietal region with surrounding edema.

primary malignancy was unremarkable. This was further confirmed by positron emission tomography (PET) CT scan which showed hypermetabolic cerebral activity corresponding to enhancing lesions seen on the MRI, but no evidence of hypermetabolic activity elsewhere in the body, favoring primary intracranial malignancy.

Stereotactic brain biopsy from the right parietal lesion was performed. A smear preparation at the time of intraoperative consultation showed a cellular proliferation with prominent vascularity (Fig. 3). Histologic preparations showed a tumor characterized by small, pleomorphic cells, present within a glial fibrillary background matrix, with regions of necrosis (Fig. 4). Areas of microvascular proliferation were also observed (Fig. 5). These findings were diagnostic of glioblastoma (WHO grade IV). Tissue was submitted for assessment of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, which was absent in the tumor, suggesting an unfavorable prognosis and predicting poor response to alkylating agents.

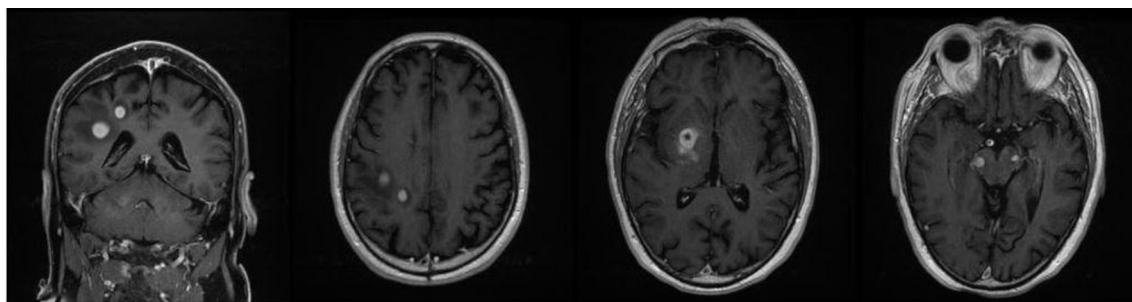
The patient was started on dexamethasone for vasogenic edema and leviracetam for seizure prophylaxis. Due to the multifocal nature of his disease, he was not felt to be a surgical candidate and was started on combined modality treatment with radiation and temozolomide. Three weeks into chemoradiation, he developed bilateral pulmonary emboli with moderate clot burden. There was

no improvement in his neurological symptoms, but he was experiencing more pain, fatigue, depression, and loss of appetite and weight. He was not satisfied with his quality of life. His repeat MRI brain showed favorable response with decreased size and enhancement of the multifocal GBM, but, due to low quality of life, he decided not to pursue any further treatment and opted for hospice care. He passed away within 4 months of diagnosis.

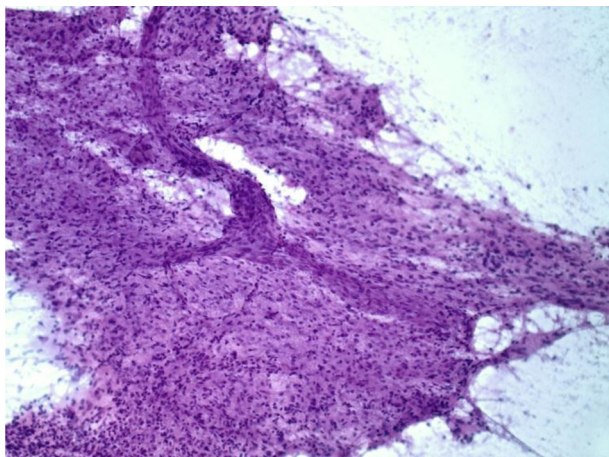
## Discussion

Brain tumors are rare when compared to other malignancies; however, they are associated with a disproportionately high mortality rate. Gliomas arise from the glial cells that surround and support the neurons. The tumor-node-metastasis (TNM) staging does not apply to gliomas as these tumors rarely metastasize to the lymph nodes or distant sites outside of the central nervous system (3).

GBMs are considered grade IV gliomas by the WHO grading system (2–4). They are considered the most malignant and aggressive of all brain tumors (1–3, 5, 6). Incidence increases with age and is about three cases per 100,000 annually in the US. Median age at diagnosis of GBM is 64 years and about 6,000 new cases occur annually in patients older than age 65 in the US. The median overall survival for patients with glioblastoma is approximately 15 months, but in patients greater than 65, median survival is reduced to 4 months, likely due to

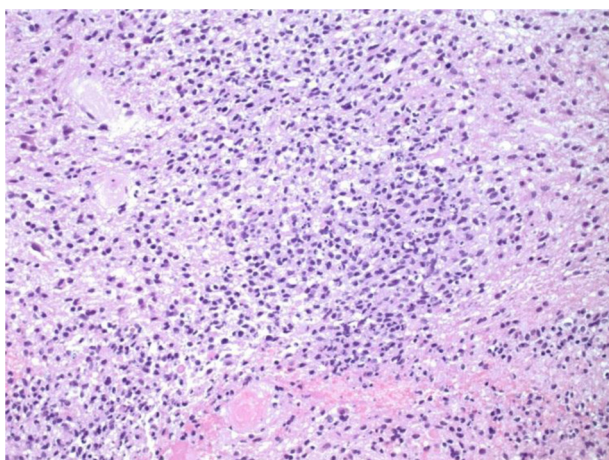


*Fig. 2.* MRI brain showing multiple enhancing lesions with surrounding edema.



*Fig. 3.* Smear preparation of the tumor, showing a cellular proliferation with prominent vascularity (H&E stain, 100x original magnification).

multiple underlying comorbidities (1, 7). Glioblastomas occur mostly in cerebral hemispheres but may occur sub-tentorially in the brainstem or cerebellum (6). A minority of cases are multifocal, mimicking brain metastases, as in our case. These are characterized by infiltrating growth, thereby making the tumor mass not clearly distinguishable from the normal tissue; however, metastasis from GBM is rare due to the protective covering from meninges, the rapid tumor growth, and short course of the disease (6). Clinical presentation depends on the location of the tumor and the anatomic structures involved (3). Common symptoms include headache, seizure, motor weakness, and focal neurological deficits like hemiparesis, aphasia, ataxia, sensory loss, hemianopia, cranial nerve dysfunction, or frequent syncope, which develop over days to weeks (3, 4). Our patient presented with recurrent falls, ataxia, left facial droop and hemiparesis, hoarse voice, dysphagia,



*Fig. 4.* Histologic section of the tumor, demonstrating a proliferation of pleomorphic, small cells, with regions of necrosis (H&E stain, 100x original magnification).

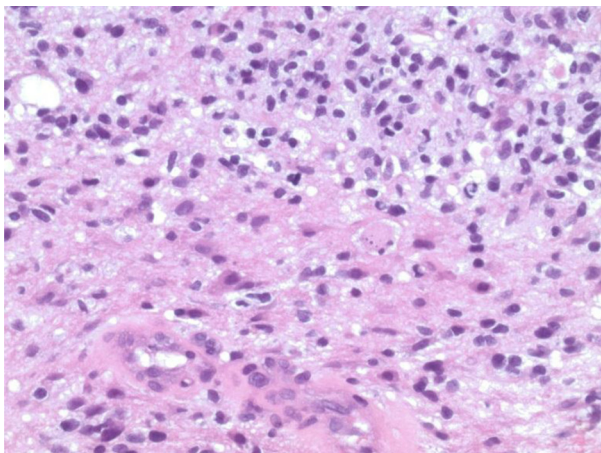
and weight loss. Rapidly growing glioblastomas may present with signs of increased intracranial pressure, such as headache associated with nausea and vomiting (3). Due to non-specific symptoms, GBM may be initially diagnosed as infection, inflammatory, circulatory or immunologic process (4).

MRI is the standard imaging modality to diagnose and monitor glioblastomas (3, 4). CT is an alternative for those who cannot undergo MRI (3). Tumor necrosis and hemorrhage on MRI are highly suggestive of glioblastoma; however, imaging findings are often non-specific and pose a challenge to differentiation from brain metastasis, as in our case (6). Definite diagnosis is made from the histopathological examination of the resected tumor or the biopsy specimen. Such tumors are highly vascular, and necrotic foci are one of their most characteristic features (4).

Treatment is multimodal, whenever possible, using surgical resection, radiation, chemotherapy, and targeted therapies with the overall goal of extending survival while maintaining quality of life (1, 3, 4, 6). Because glioblastoma has high proliferative activity and infiltrates surrounding tissues, complete resection is not always possible and radiotherapy may not always be effective (4). Nevertheless, surgical resection is the first-step treatment (1, 3). However, surgery may not always be feasible due to its location and proximity to vital structures. In such cases, biopsy is needed to establish the definitive diagnosis and the histologic tumor grade, which are essential to formulate the treatment plan (3). Our patient had multifocal glioblastoma and, hence, was not considered for surgery.

Standard treatment recommendations after resection or biopsy in the elderly population are limited by a paucity of patients over the age of 65 in clinical trials (1). Presently, following resection or biopsy, radiation therapy concurrent with daily temozolomide is pursued, followed by adjuvant monthly temozolomide, provided no tumor progression is observed (1, 3). Surgery and radiation have individually been shown to improve progression-free survival and overall survival, in the limited trials data available in the elderly population. Additionally, use of radiation has not been shown to induce cognitive decline, a frequently expressed concern by elderly patients, in subgroup analyses of patients older than 70 years, in the admittedly underpowered trials done to date (8–10). Temozolomide alone may be a reasonable alternative in elderly patients with newly diagnosed glioblastoma (1). MGMT promoter-methylated tumors have been shown to have significantly better median overall survival with administration of temozolomide (1). Our patient failed to improve symptomatically with chemoradiation, which is expected with his absence of MGMT promoter methylation within the tumor. Monoclonal antibodies such as bevacizumab, RNA interference, immunotherapy with vaccines from autologous dendritic cell, and





**Fig. 5.** High power magnification of the tumor, showing microvascular proliferation (lower, off-center to the left) (H&E stain, 200x original magnification).

hormone treatment are other treatment modalities under investigation (4). Despite combined modality treatment, recurrence is the rule and the treatment options are very limited (3). Continued research and development of new molecular and targeted immunotherapy are required for better understanding and treatment of this highly lethal tumor (2, 4).

## Conclusion

Glioblastoma (WHO grade IV) is a highly aggressive and fatal brain tumor despite aggressive treatment. It occurs, especially in the elderly population who already have multiple comorbidities and tend to do worse than the non-elderly patients. Whenever feasible, combined modality with surgery, radiation, and chemotherapy should be instituted; however, temozolomide alone may be the reasonable alternative, especially if MGMT promoter methylation is present. Further research is required for development of treatment that can prolong survival as well as ensure quality of life in the elderly population who often have multiple comorbidities.

## Conflict of interest and funding

The author/authors has/have not received any funding or benefits from industry or elsewhere to conduct this study.

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